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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,538	10/23/2003	Michele Sanicola-Nadel	BINA117CN	4018

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 03/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,538	SANICOLA-NADEL ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-48,50,58-60 and 62-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-48,50,58-60 and 62-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III, claims 43, 44, 50 and 51; and the election of SEQ ID NO:1 and the hybridoma B3F6.17 in the reply filed on 01/18/2006 is acknowledged. The traversal is on the ground(s) that the groups set forth by the Examiner all stem from a common concept and theory, and thus are related. The applicants argue that claim 43 is generic to the claims of Groups III and IV, wherein Claim 43 is directed to a method for modulating growth of tumor cells *in vivo* in a subject comprising the step of administering to the subject an effective amount of an antibody that binds Cripto, and claim 45 is directed to a method of treating a subject having a tumor, comprising administering an antibody that binds Cripto and includes the further limitation that the tumor over-expresses Cripto. Claim 43 is generic to Groups III and IV in that it embraces tumor cells generically, including cells that over-express Cripto. Applicants further argue that the inventions of Groups III and IV belong to the same search class (514) and the same subclass (2), and thus a literature search encompassing said groups would be nearly, if not completely, coextensive. In particular, Applicants submit that a search with respect to methods of modulating growth of tumor cells *in vivo* in a subject, comprising the step of administering an effective amount of an antibody that binds Cripto, would identify art relevant to the claims of Groups III and IV. In view of the relatedness of the claimed subject matter, the Applicants argue that search and examination of Groups III and IV would not constitute an undue burden to

the Examiner. In light of these arguments, Applicants propose that Groups III and IV be reformed into a single group, comprising claims 43-48, 50, 58-60, and 62-78, drawn to methods of modulating growth of tumor cells *in vivo* in a subject comprising the step of administering an antibody that binds Cripto. These arguments are found persuasive and hence the restriction requirements as set forth in the previous office action are withdrawn.

However, for the reasons as set forth in the previous office action, the species election is still maintained, and hence claims 43-48, 50, 58-60, and 62-78 are examined only to the extent that the Cripto polypeptide sequence is SEQ ID NO:1, the tumor is breast and the hybridoma producing the antibody binding to SEQ ID NO:1 is B3F6.17.

2. Claims 43, 45-48 and 58-60 have been amended

Claims 62-78 have been newly added

Claims 1-42, 49, 51-57 and 61 have been cancelled.

3. Claims 43-48, 50, 58-60, and 62-78 are under examination to the extent that the Cripto polypeptide sequence is SEQ ID NO:1, the tumor is breast and the hybridoma producing the antibody binding to SEQ ID NO:1 is B3F6.17.

Claim Objections

4. Claims 46-48, 50, 62, 70, 72, 73-78 are objected to because of the following informalities: The instant claims consist of non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43, 50, 58-60, and 62-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 is vague and indefinite for reciting "a method of modulating growth of tumor cells", because the exact meaning of the word modulate is not clear. What does the applicant mean by modulate the growth of tumor cells? Does the word, as it refers to in the claim, mean increase, decrease, inhibit, etc.? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Accordingly, the claim are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 46, 47, 62, 70, 74 and 78 are vague and indefinite for reciting ""epitope of Cripto comprised in the domain spanning amino acid residues" because the exact meaning of the word scanning is not clear. Does the applicant mean that the residues necessary for the binding of the antibody is within the particular amino acid residues claimed? As written, it is impossible for one skilled in the art to determine the metes

and bounds of the claims. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 67 is vague and indefinite for reciting "with a nonconjugated chemotherapeutic", because it is not clear as to what a nonconjugated chemotherapeutic is? Does the applicant mean a chemotherapeutic agent that is not conjugated with an antibody or that the chemotherapeutic agent can be conjugated to something other than an antibody? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claim.

Claim 76 is vague and indefinite for reciting "antibody specifically binds to a Cripto amino acid which inhibits the interaction of Cripto and ALK4", because it is exactly not clear as to how the binding of the antibody to Cripto inhibits its interaction with ALK4. Does the antibody bind to the same epitope on Cripto that ALK4 binds to; or does the binding of the antibody render the Cripto protein structurally functionless, such that Cripto becomes inactive and hence does not interact with ALK4. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48, 71, 72, 77 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of B3F6.17 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the

claimed antibody species B3F6.17. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

The specification lacks complete deposit information for the deposit of the B3F6.17 antibody. It is not clear that the B3F6.17 antibody is known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Applicant's failure to refer to the deposit information pertaining to the B3F6.17 antibody in the specification is noted and it is required that the required deposit be made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit of the B3F6.17 antibody is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of the B3F6.17 antibody has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of the B3F6.17 antibody is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits,

assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:
(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:
(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and
(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same

as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

7. Claim 78 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The amendments filed on 01/18/2006 introduced NEW MATTER into claim 78. The claim recites "wherein the antibody binds to an epitope comprised in the domain spanning amino acid residues 77-111 of SEQ ID NO:1" which is not disclosed in the specification. The response does not provide any support for the generation or utilization of antibodies that binds to the particular epitope "amino acid residues 77-111 of SEQ ID NO:1" in a method of modulating growth of tumor cells *in vivo*. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP 714.02 and 2163.06 ("Applicant

should specifically point out the support for any amendments made to the disclosure.") The specification as originally filed discloses the domain spanning residues 46-62 of Cripto-1, and the hybridoma B3F6.17. Applicants are required to specifically point our where the support for the newly added claim limitations can be found in the originally filed specification or claims or remove the limitation from the claim.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 43, 44-47, 50, 58-60, 62-70, 74, 76, 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qi et al (Journal of cancer. 1994, 69:903-910) in view of Meissner and Coleman (U.S. Patent 5981215, Date Issued: November 9, 1999)

in view of Williams et al (PGPUB 20030232755, filed March 17, 2003 but claimed priority to September 18, 2000) in view of Dan et al (U.S. Patent 6,207,153, Filed 03/27/97) and further in view of Chari et al (U.S. Patent 6333410, Date filed: August 18, 2000).

The instant claims are drawn to a method of modulating growth of tumor cells *in vivo* in a subject comprising the step of administering to the subject an effective amount of an antibody that binds Cripto and a pharmaceutically acceptable carrier, wherein the subject is human, wherein the tumor is breast, wherein the antibody is a monoclonal, humanized, human, wherein the antibody specifically binds to an epitope comprised in the domain spanning amino acid residues from about amino acid 46-62 of SEQ ID NO:1, wherein the antibody is an antibody fragment selected from Fab, F(ab') and a F(ab')2 fragment, is a full length, single chain antibody conjugated to a chemotherapeutic agent such as maytansinoid, wherein the antibody binds to a Cripto amino acid sequence shown in SEQ ID NO:1 which inhibits the interaction of Cripto and ALK4, wherein the antibody binds to an epitope comprised in the domain spanning amino acid residues 77-111 of SEQ ID NO:1.

Qi et al teach the expression of cripto-1 (CR-1) in human breast carcinomas, in addition that the breast carcinomas express multiple EGF-related peptides and show that the differential expression of CR-1 in malignant breast epithelial cells may serve as a potential tumor marker for breast cancer. Qi et al teach the CR-1 is a 188 amino acid

protein that, including the importance of the residues with the CR-1 gene, in addition to their significance to the CR-1 function; such as unlike other members of the EGF/TGF-α family, CR-1 lacks a hydrophobic signal peptide and transmembrane domain with contain central region of approximately 37 amino acids that shares structural homology with peptides within this family, and that the overexpression of CR-1 gene can lead to the in vitro transformation of mouse NIH3T3 fibroblasts or mouse NOG-8 mammary epithelial cells, demonstrating that CR-1, like TGF-a and AR, can function as an autocrine growth factor/or dominantly transforming oncogene. Qi et al also teach that the generation of an CR-1 antibody (CR-1 Ab) was generated against a 17-mer synthetic peptide that corresponds to amino acid residues 97-113 in the human CR-1 proteins that represents the carboxy terminus of the 37 amino acid EGF-like region, and that the CR-1 Ab reacts strongly with the 17-mer CR-1 peptide immunogen and the therapeutic advantages of such CR-1 antibodies (please see entire document).

Qi etl does not teach the method of modulating growth of tumor cells *in vivo* in a subject comprising the step of administering to the subject an effective amount of an antibody that binds Cripto and a pharmaceutically acceptable carrier, wherein the subject is human, wherein the tumor is breast, wherein the antibody is a monoclonal, humanized, human, wherein the antibody specifically binds to an epitope comprised in the domain spanning amino acid residues from about amino acid 46-62 of SEQ ID NO:1, wherein the antibody is an antibody fragment selected from Fab, F(ab') and a F(ab')2 fragment, is a full length, single chain antibody conjugated to a chemotherapeutic agent such as maytansinoid, wherein the antibody binds to a Cripto

amino acid sequence shown in SEQ ID NO:1 which inhibits the interaction of Cripto and ALK4, wherein the antibody binds to an epitope comprised in the domain spanning amino acid residues 77-111 of SEQ ID NO:1. However, these deficiencies are made up for by Meissner and Coleman, and Williams et al, and Dan et al and Chari et al

Meissner and Coleman (U.S. Patent 5981215, Date Issued: November 9, 1999) teach (abstract in particular) human Criptin Growth Factor polypeptide (CGF) (SEQ ID NO:7, that is 100% identical to SEQ ID NO:1 of the instant application; please see the attached sequence search). Meissner and Coleman also teaches antagonist against such polypeptides, wherein the potential CGF antagonist compounds includes antibodies, and their use as a therapeutic to treat and/or prevent neoplasia such as tumors, and, thereby competitively inhibiting the action of CGF (paragraph 70, in particular), wherein the antibody may be employed to inhibit tumor growth, directly or indirectly (paragraph 72). Meissner and Coleman also teach that the antibodies generated against the polypeptides corresponding to a sequence of the present invention can be obtained by direct injection of the polypeptides into an animal or by administering the polypeptides to an animal, preferably a nonhuman. Hence the antibody so obtained will then bind the polypeptides itself, that may bind to different epitopes depending on the polypeptide used to produce the antibody. Meissner and Coleman teach that, in this manner, even a sequence encoding only a fragment of the polypeptides can be used to generate antibodies binding the whole native polypeptides. Such antibodies can then be used to isolate the polypeptide from tissue expressing that polypeptide (paragraph 95). Meissner and Coleman teach that CGF polypeptide is over

expressed and secreted by certain types of cancer cell, for example, pancreatic cancers, and therefore detection of CGF gene transcription or an excessive amount of CGF protein allows a pancreatic cancer diagnosis. Accordingly, an anti-CGF antibody could be used to diagnose neovascularization associated with tumor formation since an altered level of this polypeptide may be indicative of such disorders (paragraph 57). Meissner and Coleman further teaches that these antibodies can be, for example, polyclonal or monoclonal antibodies including chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of an Fab expression library. (paragraph 94), and that transgenic mice may be used to express humanized antibodies to immunogenic polypeptide products (paragraph 97). In addition Meissner and Coleman teach that these antagonist antibodies of the present invention may be employed in combination with a suitable pharmaceutical carrier. Such compositions comprise a therapeutically effective amount of the polypeptide or antagonist compound and a pharmaceutically acceptable carrier or excipient. Such a carrier includes but is not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof such that the formulation should suit the mode of administration. (paragraph 75, in particular). Meissner and Coleman also teach that the pharmaceutical compositions may be administered in a convenient manner such as by the oral, topical, intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal or intradermal routes. The pharmaceutical compositions are administered in an amount which is effective for treating and/or prophylaxis of the specific indication. (paragraph 77, in particular).

Williams et al (PGPUB 20030232755, filed March 17, 2003 but claimed priority to September 18, 2000) teach Cripto polypeptide (SEQ ID NO:1 that is 100% identical to SEQ ID NO:1 of the instant application). Williams et al teach a cripto mutant which is different from that CRIPTO polypeptide, has the ability to block or inhibit CRIPTO binding to a CRIPTO binding partner, such that the Inhibition of CRIPTO binding to a CRIPTO binding partner by the cripto mutant can inhibit the growth of a tumor cell (paragraphs 63-65, in particular). Williams et al also teach that in specific embodiments, such cripto mutants which inhibit CRIPTO binding to a CRIPTO binding partner can be used as pharmaceutical compositions of the invention to treat or prevent undesired cell proliferation in subject including a subject, for example, the pharmaceutical compositions of the invention can be used therapeutically to inhibit or block growth of tumors which depend on CRIPTO protein for growth, in a particular aspect the disease or condition associated with undesired cell proliferation is cancer wherein the cancer is breast cancer (paragraph 75, in particular). In summary, Williams teach that the growth of tumors which depend on CRIPTO protein for growth can be inhibited or blocked by a molecule (in this particular case cripto mutants) that inhibits CRIPTO binding to a CRIPTO binding partner

Dan et al teach a monoclonal antibody H11 and antigen binding fragments that specifically bind to the antigen recognized by H11, the C-antigen, which is found specifically on neoplastic cells and not on normal cells (abstract in particular), wherein the antigen binding polypeptide fragment is selected from the group consisting of whole antibodies, antibodies, chimeric antibodies, Fab, F(ab), F(ab')2, full length, single chain

V region fragments (scFv) including the conjugation of the antibodies to a chemically functional moiety such as modifiers, toxins, detectable labels, paramagnetic labels, and drugs (claim 15 and 16, in particular); and the therapeutic advantages of such single chain or fragment antibodies that are conjugated, including to a chemotherapeutic agent (brief description of the invention, in particular).

Chari et al (U.S. Patent 6333410, Date filed: August 18, 2000). Chari et al teach antibody drug-conjugates utilizing Maytansinoids as a conjugate (see brief summary of the invention, in particular) and the evaluation of such antibodies in humans.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of modulating growth of tumor cells *in vivo* in a subject comprising the step of administering to the subject an effective amount of an antibody that binds Cripto and a pharmaceutically acceptable carrier, wherein the subject is human, wherein the tumor is breast, wherein the antibody is a monoclonal, humanized, human, wherein the antibody specifically binds to an epitope comprised in the domain spanning amino acid residues from about amino acid 46-62 of SEQ ID NO:1, wherein the antibody is an antibody fragment selected from Fab, F(ab') and a F(ab')2 fragment, is a full length, single chain antibody conjugated to a chemotherapeutic agent such as maytansinoid, wherein the antibody binds to a Cripto amino acid sequence shown in SEQ ID NO:1 which inhibits the interaction of Cripto and ALK4, wherein the antibody binds to an epitope comprised in the domain spanning amino acid residues 77-111 of SEQ ID NO:1.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the antibodies to cripto-1 for therapeutic advantages, specifically in breast tumor, based on the teachings of Qi et al and Meissner and Coleman because Qi et al teach the expression of cripto-1 in human breast carcinomas, in addition that the breast carcinomas express multiple EGF-related peptides and show that the differential expression of CR-1 in malignant breast epithelial cells may serve as a potential tumor marker for breast cancer including the generation of an CR-1 antibody (CR-1 Ab) generated against a 17-mer synthetic peptide that corresponds to amino acid residues 97-113 in the human CR-1 proteins that represents the carboxy terminus of the 37 amino acid EGF-like region, and that the CR-1 Ab reacts strongly with the 17-mer CR-1 peptide immunogen and the therapeutic advantages of such CR-1 antibodies and because Meissner and Coleman teach a teach human Criptin Growth Factor polypeptide (CGF) (SEQ ID NO:7, that is 100% identical to SEQ ID NO:1 of the instant application and that these CGF polypeptides are over expressed and secreted by certain types of cancer cell, for example, pancreatic cancers, and therefore detection of CGF gene transcription or an excessive amount of CGF protein allows a pancreatic cancer diagnosis, and accordingly, an anti-CGF antibody could be used to diagnose neovascularization associated with tumor formation since an altered level of this polypeptide may be indicative of such disorders.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have combined the teachings of Qi et l

a with the teachings of Meissner and Coleman because Qi et al teach the CR-1 is a 188 amino acid protein that, unlike other members of the EGF/TGF-α family, lacks a hydrophobic signal peptide and transmembrane domain with contain central region of approximately 37 amino acids that shares structural homology with peptides within this family, and that the overexpression of CR-1 gene can lead to the in vitro transformation of mouse NIH3T3 fibroblasts or mouse NOG-8 mammary epithelial cells, demonstrating that CR-1, like TGF-a and AR, can function as an autocrine growth factor/or dominantly transforming oncogene, and Meissner and Coleman teach a human Criptin Growth Factor polypeptide (CGF) (SEQ ID NO:7, that is 100% identical to SEQ ID NO:1 of the instant application, in addition to antagonist against such polypeptides, wherein the potential CGF antagonist compounds includes antibodies, and their use as a therapeutic to treat and/or prevent neoplasia such as tumors, and, thereby competitively inhibiting the action of CGF, wherein the antibody may be employed to inhibit tumor growth, directly or indirectly, possibly by blocking the interaction between Cr-1 and ALK4,

Moreover, one of ordinary skill in the art would have known to have developed a method of modulating cells *in vivo* in a subject from the teachings of Qi et al, Meissner and Coleman and Williams et al because Qi et al teach the expression of cripto-1 in human breast carcinomas, and because Meissner and Coleman teach antagonists to CGF wherein the CGF antagonist compounds includes antibodies, wherein the antibody may be employed to inhibit tumor growth, directly or indirectly, and because Williams et al teach CRIPTO polypeptide (SEQ ID NO:1 that is 100% identical to SEQ ID NO:1 of

the instant application), including a specific cripto mutant which is different from that CRIPTO polypeptide, that has the ability to block or inhibit CRIPTO binding to a CRIPTO binding partner, such that the inhibition of CRIPTO binding to a CRIPTO binding partner by the cripto mutant can inhibit the growth of a tumor cell, in addition, Williams et al also teach that in specific embodiments, such cripto mutants which inhibit CRIPTO binding to a CRIPTO binding partner can be used as pharmaceutical compositions of the invention to treat or prevent undesired cell proliferation in subject including a subject, for example, the pharmaceutical compositions of the invention can be used therapeutically to inhibit or block growth of tumors which depend on CRIPTO protein for growth, in a particular aspect the disease or condition associated with undesired cell proliferation is cancer wherein the cancer is breast cancer.

Furthermore, one of ordinary skill in the art would have known to have Combined the above teachings of Qi et al, Meissner and Coleman and Williams et al because Qi et al teach the expression of cripto-1 in human breast carcinomas including the importance of the residues with the CR-1 gene, in addition to their significance to the CR-1 function, and because Meissner and Coleman teach antagonists to CGF wherein the CGF antagonist compounds includes antibodies which may be employed to inhibit tumor growth, directly or indirectly; in addition to teaching that the antibodies, for example, polyclonal or monoclonal antibodies including chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of an Fab expression library, that may bind to different epitopes depending on the polypeptide used to produce the antibody, can be generated against the polypeptides corresponding to a sequence of

the present invention can be obtained by direct injection of the polypeptides into an animal or by administering the polypeptides to an animal, preferably a nonhuman. In addition, Meissner and Coleman teach that, in this manner, even a sequence encoding only a fragment of the polypeptides (for example the 46-62 of SEQ ID NO:1 or 114-150 of SEQ ID NO:1 or 77-111 of SEQ ID NO:1 because Qi et al teach the residues and the importance of these residues within CR-1 gene, in addition to their significance to the CR-1 function) can be used to generate antibodies binding the whole native polypeptides, , in addition to blocking the interaction between Cr-1 and ALK4, further that transgenic mice may be used to express humanized antibodies to immunogenic polypeptide products, and that the antibodies of the invention may be employed in combination with a suitable pharmaceutical carrier, such as a therapeutically effective amount of the polypeptide or antagonist antibody compound and a pharmaceutically acceptable carrier or excipient, wherein the pharmaceutical compositions are administered in an amount which is effective for treating and/or prophylaxis of the specific indication, and because Williams et al teach a CRIPTO polypeptide (100% identical to SEQ ID NO:1 of the instant application), including a specific cripto mutant specific cripto mutant which is different from that CRIPTO polypeptide, that has the ability to block or inhibit CRIPTO binding to a CRIPTO binding partner, such that the inhibition of CRIPTO binding to a CRIPTO binding partner by the cripto mutant can inhibit the growth of a tumor cell.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced a method of

modulating growth of tumor cells *in vivo* in a subject comprising the step of administering to the subject an effective amount of an antibody that binds Cripto and a pharmaceutically acceptable carrier, wherein the subject is human, wherein the tumor is breast comprising all the limitations because by combining the teachings of Qi et al, Meissner and Coleman and Williams et al along with Dan et al and Chari et al because Dan et al teach that an antigen binding polypeptide fragment, an antibody, that can be used in therapeutic purposes wherein the antigen binding polypeptide fragment is selected from the group consisting of monoclonal antibodies, whole antibodies, chimeric antibodies, Fab, F(ab), F(ab')2, full length, single chain V region fragments (scFv) including the conjugation of the antibodies to a chemically functional moiety such as modifiers, toxins, detectable labels, paramagnetic labels, and drugs and the therapeutic advantages of such single chain or fragment antibodies that are conjugated, including to a chemotherapeutic agent, and because Chari et al teach antibody drug-conjugates utilizing Maytansinoids as a conjugate and the evaluation of such antibodies in humans,

Thus it would have been obvious to one skilled in the art to produced a method of modulating growth of tumor cells *in vivo* in a subject comprising the step of administering to the subject an effective amount of an antibody that binds Cripto and a pharmaceutically acceptable carrier, wherein the subject is human, wherein the tumor is breast because it is well known in the art prior to the filing date of the instant application that CR-1 protein was associated with the breast cancer as taught by Qi et al (in 1994) and that the antibodies or blocking agents of the function of CR-1 can have therapeutic advantages in the treatment and/or prophylaxis of breast tumors as taught by Meissner

and Coleman and Williams et al, wherein the antibody can be a monoclonal, humanized, human, wherein the antibody specifically binds to an epitope comprised in the domain spanning amino acid residues from about amino acid 46-62 of SEQ ID NO:1, wherein the antibody is an antibody fragment selected from Fab, F(ab') and a F(ab')2 fragment, is a full length, single chain antibody conjugated to a chemotherapeutic agent such as maytansinoid, wherein the antibody binds to a Cripto amino acid sequence shown in SEQ ID NO:1 which inhibits the interaction of Cripto and ALK4, wherein the antibody binds to an epitope comprised in the domain spanning amino acid residues 77-111 of SEQ ID NO:1.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 43-48, 50, 58-60 and 62-78 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88-104 of copending Application No. 10/945,853. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the reasons stated below.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 43-48, 50, 58-60 and 62-78 of the instant application are drawn to a method of modulating growth of tumor cells in vivo in a subject comprising the step of administering to the subject an effective amount of a composition comprising an antibody that binds to Cripto and a Pharmaceutically acceptable carrier, wherein the subject is human. In addition, the methods are drawn to a method of treating a subject having a tumor that over-expresses CRIPTO comprising administering to the subject a composition comprising an antibody that binds to Cripto and a pharmaceutically acceptable carrier in an effective amount. In addition, the claims are drawn to a method of treating a subject having a tumor that over-expresses Cripto comprising administering to the subject a composition comprising an antibody that specifically binds to an epitope of Cripto comprised in the domain spanning amino acid residues from about amino acid 46 to about amino acid 62 of SEQ ID NO:1 in an effective amount, and domain

spanning amino acid residues from about amino acid 114 to about amino acid 150 of SEQ ID NO:1 in an effective amount, further comprising an antibody, which binds specifically to an epitope, produced by the hybridoma B3F6.17. The claims are further drawn to a method of modulating growth of tumor cells in vivo in a subject wherein the tumor is breast, wherein the antibody is monoclonal, humanized, human. The claims further recite the method wherein the antibody specifically binds to an epitope of Cripto comprised in the domain spanning amino acid residues from about amino acid 46 to about amino acid 62 of SEQ ID NO:1, wherein the antibody is an antibody fragment selected from the group consisting of a Fab, a Fab', and a F(ab')2 fragment, full length antibody, single chain antibody, wherein the antibody is conjugated to a chemotherapeutic agent, wherein the antibody is administered in combination with a nonconjugated chemotherapeutic, wherein the chemotherapeutic agent is selected from the group consisting of a tumor-activated prodrug, a radionuclide and a toxin, wherein the tumor-activated prodrug is a maytansinoid, wherein the antibody specifically binds to an epitope comprised in the domain spanning amino acid residues from about amino acid 46-62 of SEQ ID NO:1 which antibody is conjugated to a maytansinoid and a pharmaceutically acceptable carrier, wherein the antibody is produced by the hybridoma B3F6.17, wherein the antibody sspecifically binds to a Cripto amino acid sequence shown in SEQ ID NO:1 which is capable of internalizing Cripto, wherein the antibody specifically binds to an epitope comprised in the cysteine-rich domain of Cripto spanning from about 114 to about amino acid 150 of SEQ ID NO:1, wherein the

antibody specifically binds to a Cripto amino acid sequence shown in SEQ ID NO:1 and which inhibits the interaction of Cripto and ALK4.

Claims 88-104 of copending Application No. 10/945,853 are drawn a method of decreasing tumor growth in vivo comprising contacting a cell with a composition comprising an antibody which is specific for an epitope of Cripto comprised in the domain spanning amino acid residues from about amino acid 46 to about amino acid 62 of SEQ ID NO:1, or an antibody which is specific for the cysteine-rich domain of Cripto spanning from about amino acid residue 114 to about amino acid residue 150 of SEQ ID NO:1, and a pharmaceutically acceptable carrier, wherein the tumor cell is breast. Further, the claims are drawn to a method of inhibiting angiogenesis comprising administering an antibody that specifically binds to a Cripto amino acid sequence shown in SEQ ID NO:1 to a subject having a tumor, wherein the antibody specifically binds to an epitope comprised in the cysteine-rich domain of Cripto spanning from about amino acid residue 114 to about amino acid residue 150 of SEQ ID NO:1, or the domain spanning amino acid residues from about amino acid 46 to about amino acid 62 of SEQ ID NO:1, wherein the antibody is an antibody fragment selected from the group consisting of a Fab, a Fab', and a F(ab')2 fragment, wherein the antibody is a full length antibody, single chain antibody, is conjugated to a chemotherapeutic agent, wherein the antibody is administered in combination with a nonconjugated chemotherapeutic, wherein the chemotherapeutic agent is selected from the group consisting of a tumor-activated prodrug, a radionuclide and a toxin, wherein the chemotherapeutic agent is a

tumor-activated prodrug, wherein the tumor-activated prodrug is a maytansinoid, wherein the antibody is human, wherein the antibody is monoclonal, wherein the antibody is humanized and wherein the antibody is humanized B3F6.17.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of modulating growth of tumor cells in vivo in a subject comprising the step of administering to the subject an effective amount of a composition comprising an antibody that binds to Cripto and a Pharmaceutically acceptable carrier or treating a subject having a tumor that over-expresses Cripto comprising administering to the subject a composition comprising an antibody that specifically binds to an epitope of Cripto as taught by claims 88-104 of the copending Application No. 10/945,853.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced a method of modulating growth of tumor cells in vivo or a method of treating a subject having a tumor, wherein the tumor is breast, that over-expresses CRIPTO comprising the step of administering to the subject an effective amount of a composition comprising an antibody that binds to Cripto and a pharmaceutically acceptable carrier, wherein the subject is human as taught by claims 88-90 of US '853, because claims 88-90 of US '853 teach a method of decreasing tumor growth in vivo, wherein the tumor cell is selected from breast, comprising contacting a cell with a composition comprising an antibody which is specific

for an epitope of Cripto and a pharmaceutically acceptable carrier to a subject (which can be human as evidenced by the specification in paragraph 28).

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced a method of modulating growth of tumor cells in vivo or a method of treating a subject having a tumor comprising the step of administering to the subject an effective amount of a composition comprising an antibody that binds to Cripto that specifically binds to the domain spanning amino acid residues from about amino acid 46-62 of SEQ ID NO;1 in an effective amount, or a domain spanning amino acid residues from about amino acid 114-150 of SEQ ID NO:1 in an effective amount, further comprising an antibody, which binds specifically to an epitope, produced by the hybridoma B3F6.17, wherein the antibody is an antibody fragment selected from the group consisting of a Fab, a Fab', and a F(ab')2 fragment, full length antibody, single chain antibody, wherein the antibody is conjugated to a chemotherapeutic agent, wherein the antibody is administered in combination with a nonconjugated chemotherapeutic, wherein the chemotherapeutic agent is selected from the group consisting of a tumor-activated prodrug, a radionuclide and a toxin, wherein the tumor-activated prodrug is a maytansinoid as taught by claims 91-104 of US '853, because claims 91-104 of US '853 teach a method of decreasing tumor growth in vivo comprising contacting a cell with a composition comprising an antibody which is specific for an epitope of Cripto that specifically binds to the domain spanning amino acid residues from about amino acid 46-62 of SEQ ID NO:1, or an antibody which is specific for the cysteine-rich domain of Cripto spanning from about

amino acid residue 114-150 of SEQ ID NO:1, and a pharmaceutically acceptable carrier wherein the antibody is an antibody fragment selected from the group consisting of a Fab, a Fab', and a F(ab')2 fragment, wherein the antibody is a full length antibody, single chain antibody, is conjugated to a chemotherapeutic agent, wherein the antibody is administered in combination with a nonconjugated chemotherapeutic, wherein the chemotherapeutic agent is selected from the group consisting of a tumor-activated prodrug, a radionuclide and a toxin, wherein the chemotherapeutic agent is a tumor-activated prodrug, wherein the tumor-activated prodrug is a maytansinoid, wherein the antibody is human, wherein the antibody is monoclonal, wherein the antibody is humanized and wherein the antibody is humanized B3F6.17.

Moreover, one of ordinary skill in the art would have known to have produced a method of modulating growth of tumor cells in vivo or a method of treating a subject having a tumor antibody specifically binds to an epitope of Cripto comprised in the domain spanning amino acid residues from about amino acid 46-62 of SEQ ID NO:1 or, wherein the antibody specifically binds to an epitope comprised in the domain spanning amino acid residues from about amino acid 114-150 of SEQ ID NO:1 or wherein the antibody specifically binds to a Cripto amino acid sequence shown in SEQ ID NO:1 which inhibits the interaction of Cripto and ALK4 as taught by claims 88-92 and 104 of US '853, because claims 88-92 and 104 of US '853 teach a method of inhibiting angiogenesis comprising administering an antibody that specifically binds to a Cripto amino acid sequence shown in SEQ ID NO:1 to a subject having a tumor, wherein the antibody specifically binds to an epitope comprised in the cysteine-rich domain of Cripto

spanning from about amino acid residue 114-150 of SEQ ID NO:1, or the domain spanning amino acid residues from about amino acid 46-62 of SEQ ID NO:1, as evidenced by the specification of US '853 in paragraph 8, the antibody produced by the hybridoma B3F6.17 binds to Cripto and blocks the interaction between Cripto and ALK4, and that the antibody is capable of binding domain of the Cripto protein spanning residue 75 to about residue 112 (paragraph 0042 of US '853).

Thus it would have been obvious to one skilled in the art, would have been motivated and would have had a reasonable expectation of success to have produced a method of modulating growth of tumor cells in vivo in a subject comprising the step of administering to the subject an effective amount of a composition comprising an antibody that binds to Cripto and a Pharmaceutically acceptable carrier or treating a subject having a tumor that over-expresses Cripto comprising administering to the subject a composition comprising an antibody that specifically binds to an epitope of Cripto.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

13. No claims are allowed

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is

571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER